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(54) **Title:** 8-OXOADENINE DERIVATIVES ACTING AS MODULATORS OF TLR7

(57) **Abstract:** The present invention provides 8-oxoadenine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy. The 8-oxoadenine derivatives act as modulators of Toll-like Receptor (TLR) 7 and thus may be used in the treatment of asthma, hepatitis, allergic diseases, viral and bacterial infection as well as cancer.

WO 2008/004948 A1

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The present invention relates to adenine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

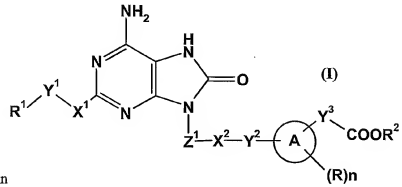
The immune system is comprised of innate and acquired immunity, both of which work cooperatively to protect the host from microbial infections. It has been shown that innate immunity can recognize conserved pathogen-associated molecular patterns through toll-like receptors (TLRs) expressed on the cell surface of immune cells. Recognition of invading pathogens then triggers cytokine production (including interferon alpha(IFNα)) and upregulation of co-stimulatory molecules on phagocytes, leading to modulation of T cell function. Thus, innate immunity is closely linked to acquired immunity and can influence the development and regulation of an acquired response.

TLRs are a family of type I transmembrane receptors characterized by an NH_2-terminal extracellular leucine-rich repeat domain (LRR) and a COOH-terminal intracellular tail containing a conserved region called the Toll/IL-1 receptor (TIR) homology domain. The extracellular domain contains a varying number of LRR, which are thought to be involved in ligand binding. Eleven TLRs have been described to date in humans and mice. They differ from each other in ligand specificities, expression patterns, and in the target genes they can induce.

Ligands which act via TLRs (also known as immune response modifiers (IRMS)) have been developed, for example, the imidazoquinoline derivatives described in US Patent No. 4689338 which include the product Imiquimod for treating genital warts, and the adenine derivatives described in WO 98/01448 and WO 99/28321.

This patent application describes a class of 9-substituted-8-oxoadenine compounds having immuno-modulating properties which act via TLR7 that are useful in the treatment of viral or allergic diseases and cancers.

In accordance with the present invention, there is therefore provided a compound of formula (I)



(I)

wherein

R^1 represents hydrogen, hydroxyl, or a C_1-C_6 alkoxy, C_2-C_5 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_6-C_{10} aryl, C_5-C_{10} heteroaryl or C_3-C_8 cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, a C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_2-C_5 alkoxycarbonyl, amino (NH_2), (mono)- C_1-C_6 alkylamino and (di)-C_1-C_6 alkylamino group;

Y^1 represents a single bond or C_1-C_6 alkylene;

X^1 represents a single bond, an oxygen, sulphur atom, sulphonyl (SO_2) or NR^3;

Z^1 represents a C_2-C_6 alkylene or C_3-C_8 cycloalkylene group, each group being optionally substituted by at least one hydroxyl;

X^2 represents NR^4;

Y^2 represents a single bond or C_1-C_6 alkylene;

Y^3 represents a single bond or C_1-C_6 alkylene;

n is an integer 0, 1 or 2;

R represents halogen or a C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 haloalkoxy, amino (NH_2), (mono)-C_1-C_6 alkylamino, (di)-C_1-C_6 alkylamino group or a C_3-C_8 saturated heterocyclic ring

comprising a ring nitrogen atom and optionally one or more further heteroatoms independently selected from nitrogen, oxygen and sulphur, the heterocyclic ring being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_5 alkylcarbonyl and C_2-C_5 alkoxycarbonyl;

R^2 represents hydrogen or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_8 cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, hydroxyl or a C_1-C_6 alkoxy, C_2-C_{10} acyloxy, amino (NH_2), (mono)- C_1-C_6 alkylamino, (di)-C_1-C_6 alkylamino group and a C_3-C_8 saturated heterocyclic ring comprising a ring nitrogen atom and optionally one or more further heteroatoms independently selected from nitrogen, oxygen and sulphur, the heterocyclic ring in turn being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_5 alkylcarbonyl and C_2-C_5 alkoxycarbonyl group;

R^3 represents hydrogen or C_1-C_6 alkyl;

R^4 represents CO_2R^5, SO_2R^5, COR^5, $SO_2NR^6R^7$ and $CONR^6R^7$;

R^5 independently represents

(i) a 3- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms comprising ring group NR^8, $S(O)_m$ or oxygen, each ring may being optionally substituted by one or more substituents independently selected from halogen, hydroxyl or a C_1-C_6 alkyl and C_1-C_6 alkoxy group, or

(ii) a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, cyano, C_1-C_6 alkyl, C_1-C_3 haloalkyl, carboxyl, $S(O)_mR^9$, OR^{10}, CO_2R^{10}, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}SO_2R^9$, $NR^{10}CO_2R^9$, $NR^{10}COR^9$, or

(iii) a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_8 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, CN, C_3-C_8 cycloalkyl, $S(O)_pR^{12}$, OR^{13}, COR^{13}, CO_2R^{13}, $SO_2NR^{13}R^{14}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, $NR^{13}SO_2R^{12}$ or a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group or a heterocyclic ring, the latter three groups may be optionally substituted by one or more substituents independently selected from C_1-C_6 alkyl (optionally substituted by hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, amido, C_1-C_6 alkylamido, di-C_1-C_6 alkylamido, $-OCH_2CH_2OH$, pyrrolidinyl, pyrrolidinylcarbonyl, furanyl, piperidyl, methylpiperidyl or phenyl), C_1-C_6 alkenyl (optionally substituted by phenyl), halogen, hydroxy, cyano, carboxy, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, amido, C_1-C_6 alkylamido, di-C_1-C_6 alkylamido, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylsulphonyl, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylcarbonylmethylamino, phenyl (optionally substituted by hydroxy, fluoro or methyl), pyrrolidinyl, pyridyl, piperidinyl, benzothiazolyl or pyrimidinyl;

R^6 represents hydrogen or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl group or heterocyclic ring, each of which may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, OR^{15}, $S(O)_qR^{15}$, CO_2R^{16}, COR^{16}, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}COR^{17}$, $NR^{16}CO_2R^{15}$, $SO_2NR^{16}R^{17}$, $NR^{16}SO_2R^{15}$, or a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group or heterocyclic ring, the latter three groups being optionally substituted by one or more substituents independently selected from, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, halogen, $S(O)_qR^{15}$, CO_2R^{16}, COR^{16}, hydroxy or cyano; and

R^7 represents hydrogen, a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_8 cycloalkyl group, each group may be optionally substituted by one or more

substituents independently selected from halogen, C_3-C_8 cycloalkyl, a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group, carboxy, cyano, OR^{15}, hydroxy or $NR^{18}R^{19}$, or

R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated or partially saturated heterocyclic ring, optionally containing further heteroatoms or heterogroups selected from nitrogen, $S(O)_m$ or oxygen. The heterocyclic ring, may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR^{20}, $NR^{21}R^{22}$, $S(O)_qR^{23}$, COR^{24}, CO_2R^{24}, $NR^{24}R^{25}$, $CONR^{24}R^{25}$, $NR^{24}COR^{25}$, $NR^{24}CO_2R^{23}$, $SO_2NR^{24}R^{25}$, $NR^{24}SO_2R^{23}$, C_6-C_{10} aryl, C_5-C_{10} heteroaryl group, heterocyclic ring, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_8 cycloalkyl group, the latter seven groups being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, cyano, OR^{20}, $S(O)_qR^{23}$, COR^{24}, CO_2R^{24}, $NR^{24}R^{25}$, $CONR^{24}R^{25}$, $NR^{24}CO_2R^{23}$, $NR^{24}COR^{25}$, $SO_2NR^{24}R^{25}$, $NR^{24}SO_2R^{23}$, a heterocyclic ring or a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group, the latter three groups being optionally substituted by one or more substituents independently selected from C_1-C_6 alkyl, halogen, hydroxy or cyano;

R^8 represents hydrogen, CO_2R^{26}, COR^{26}, SO_2R^{26}, C_1-C_6 alkyl or C_3-C_6 cycloalkyl group, each group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, and $NR^{27}R^{28}$;

R^{10}, R^{11}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{26}, R^{27}, R^{28}, R^{29} or R^{30} each independently represents hydrogen, and a C_1-C_6 alkyl or C_3-C_6 cycloalkyl group;

R^{24} and R^{25} each independently represents hydrogen, and a C_1-C_6 alkyl or C_3-C_6 cycloalkyl group; or

R^{24} and R^{25} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated or partially saturated heterocyclic ring, optionally containing further heteroatoms or heterogroups selected from nitrogen, $S(O)_m$ or oxygen;

R^9, R^{12}, R^{15} and R^{23} represent C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R^{13} and R^{14} are defined as for R^6 and R^7 respectively;

R^{20} represents a C_1-C_6 alkyl optionally substituted by one or more substituents independently selected from halogen, hydroxyl or OR^{23};

m, p, q and r each independently represent an integer 0, 1 or 2; and

A represents a C_6-C_{10} aryl or C_5-C_{12} heteroaryl group;

or a pharmaceutically acceptable salt thereof.

In the context of the present specification, unless otherwise stated, an alkyl substituent group or an alkyl moiety in a substituent group may be linear or branched. Examples of C_1-C_6 alkyl groups/moieties include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl and n-hexyl. Similarly, an alkylene group/moiety may be linear or branched. Examples of C_1-C_6 alkylene groups/moieties include methylene, ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, 1-methylethylene, 2-methylethylene, 1,2-dimethylethylene, 1-ethylethylene, 2-ethylethylene, 1-, 2- or 3-methylpropylene and 1-, 2- or 3-ethylpropylene. A C_1-C_6 haloalkyl or C_1-C_6 haloalkoxy substituent group/moiety will comprise at least one halogen atom, e.g. one, two, three, four or five halogen atoms, examples of which include trifluoromethyl, trifluoromethoxy or pentafluoroethyl. The alkyl groups in a di-C_1-C_6 alkylamino group/moiety may be the same as, or different from, one another. A C_1-C_6 hydroxyalkyl or C_1-C_6 hydroxyalkoxy substituent group/moiety will comprise at least one hydroxyl group, e.g. one, two or three hydroxyl groups. An aryl or heteroaryl substituent group/moiety may be monocyclic or polycyclic (e.g. bicyclic or tricyclic) in which the two or more rings are fused. A heteroaryl group/moiety will comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur. Examples of aryl and heteroaryl groups/moieties include phenyl, 1-naphthyl, 2-naphthyl, furyl, thienyl, pyrrolyl, pyridyl, indolyl, isoindolyl, quinolyl, isoquinolyl, pyrazolyl, imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiazolyl and oxazolyl. A heterocyclic ring is defined as a saturated or partially saturated 3-8 membered ring containing at least one hetero

atom or group selected from nitrogen, sulphur, SO, SO_2 or oxygen. The ring may be fused with a C_6-C_{10} aryl or C_5-C_{12} heteroaryl group. Examples include morpholine, azetidine, pyrrolidine, piperidine, piperazine, 3-pyrroline, isoindoline, tetrahydroquinoline and thiomorpholine.

A C_2-C_{10} acyloxy group/moiety is exemplified by a C_2-C_5 alkylcarbonyloxy group, a C_2-C_5 alkenylcarbonyloxy group, a C_2-C_5 alkynylcarbonyloxy group, a C_6-C_9 arylcarbonyloxy group or a C_5-C_9 heteroarylcarbonyloxy group, each of which may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, C_1-C_3 alkoxy or phenyl providing that the total number of carbon atoms in the acyloxy group does not exceed 10.

Preferably X^1 represents oxygen.

Preferably Y^1 represents C_1-C_6 alkylene and R^1 represents hydrogen

Preferably Z^1 represents C_2-C_6 alkylene, more preferably $(CH_2)_3$.

Preferably Y^2 represents C_1-C_6 alkylene, more preferably a CH_2 group.

Preferably A represents a C_6-C_{10} aryl, more preferably phenyl.

Preferably Y^3 represents C_1-C_6 alkylene, more preferably CH_2.

Preferably R^2 represents C_1-C_6 alkyl more preferably methyl.

Preferably R^4 represents SO_2R^5 or COR^5.

Examples of compounds of the invention include:

Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(4-methylpiperazin-1-yl)acetyl]amino}methyl)phenyl]acetate,

Methyl (4-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](*N*,*N*-dimethylglycyl)amino]methyl}phenyl)acetate,

Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate,

Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][4-(dimethylamino)butanoyl]amino}methyl)phenyl]acetate,

Methyl (4-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](*N*,*N*-dimethyl-β-alanyl)amino]methyl}phenyl)acetate,

Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][*N*,*N*-bis(2-hydroxyethyl)glycyl]amino}methyl)phenyl]acetate,

Methyl {4-[([3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]{[4-(2-hydroxyethyl)piperazin-1-yl]acetyl}amino)methyl]phenyl}acetate,

Methyl {4-[([3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]{[4-(methylsulfonyl)piperazin-1-yl]acetyl}amino)methyl]phenyl}acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate,

Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](glycyl)amino]methyl}phenyl)acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(methylthio)acetyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(methylsulfinyl)acetyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(methylsulfonyl)acetyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylthio)propanoyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylsulfonyl)propanoyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][*N*-(methylsulfonyl)glycyl]amino}methyl)phenyl]acetate,

tert-Butyl 4-{[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-4-oxobutanoate,

4-{[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-4-oxobutanoic acid,

Methyl 3-{[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-3-oxopropanoate,

Methyl [3-({acetyl[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]amino}methyl)phenyl]acetate,

Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](methylsulfonyl)amino]methyl}phenyl)acetate,

(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)[2R]-propyl]-(pyrrolidine-2-carbonyl)-amino]-methyl}-phenyl)-acetic acid methyl ester,

(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)-propyl][2S,4R](4-hydroxy-pyrrolidine-2-carbonyl)-amino]-methyl}-phenyl)-acetic acid methyl ester,

(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)-propyl][2S]-(1-methyl-pyrrolidine-2-carbonyl)-amino]-methyl}-phenyl)-acetic acid methyl ester,

(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)-propyl]-(3-piperazin-1-yl-propionyl)-amino]-methyl}-phenyl)-acetic acid methyl ester,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7*H*-purin-9-yl)propyl-[2-[4-[3-(1-piperidyl)propyl]piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[3-(diethylcarbamoyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-phenyl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7*H*-purin-9-yl)propyl-[2-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Ethyl 4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]piperazine-1-carboxylate,

2-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-(2-cyanoethyl)amino]acetic acid,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(benzyl-(2-dimethylaminoethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-carbamoyl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(3R)-3-hydroxypyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

tert-Butyl (2S)-1-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]pyrrolidine-2-carboxylate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(2-cyanoethyl-(oxolan-2-ylmethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(pyridin-4-ylmethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-ethylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(methyl-(2-pyridin-4-ylethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyrrolidin-1-yl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-carbamoylpyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(3,6-dihydro-2H-pyridin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(2-hydroxyethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(cyclohexyl-(2-hydroxyethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(hydroxymethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-aminoethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-hydroxyethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[methyl-(1-methyl-4-piperidyl)amino]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-benzyl-4-hydroxy-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-cinnamylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(3-dimethylaminopropyl-methyl-amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(dimethylcarbamoylmethyl-methyl-amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2R)-2-carbamoylpyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-methyl-1,4-diazepan-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-morpholin-4-ylacetyl)amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(3-hydroxyphenyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[[2-[3-(acetyl-methyl-amino)pyrrolidin-1-yl]acetyl]-[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(3S)-3-dimethylaminopyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyridin-4-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(3-dimethylaminopropyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-propan-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(dimethylcarbamoylmethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2-hydroxy-2-phenyl-ethyl)-methyl-amino]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(aminomethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(methyl-(2-methylaminoethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-thiomorpholin-4-ylacetyl)amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-phenylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(1,3-dihydroisoindol-2-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-piperazin-1-ylacetyl)amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(1-piperidyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyridin-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-hydroxy-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(4-fluorophenyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-methyl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(2,5-dihydropyrrol-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-benzothiazol-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(ethoxycarbonylmethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-dimethylaminoethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-methylphenyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-ethylsulfonylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

(2S,4R)-1-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]-4-hydroxy-pyrrolidine-2-carboxylic acid,

(2S)-2-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-methyl-amino]-3-phenyl-propanoic acid,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

3-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-(1,1-dioxothiolan-3-yl)amino]propanoic acid,

3-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-cyclohexyl-amino]propanoic acid,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(2-ethylaminoethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(3-ethylaminopropyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(3,4-dihydro-1H-isoquinolin-2-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-[(1-methyl-4-piperidyl)methyl]piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(methyl-prop-2-ynyl-amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(1-methyl-4-piperidyl)-phenethyl-amino]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(oxolan-2-ylmethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(3R)-3-aminopyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

tert-Butyl (2R)-1-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]pyrrolidine-2-carboxylate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyrimidin-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-pyrrolidin-1-ylacetyl)amino]methyl]phenyl]acetate,

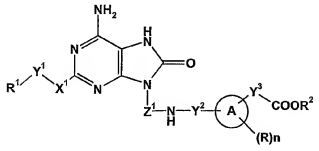
Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

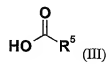
and pharmaceutically acceptable salts thereof.

The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined above which comprises,

(a) when R^4 represents COR^5, reacting a compound of formula (II)



(II)

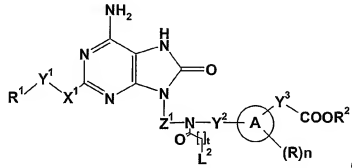


(III)

wherein n, A, Y^1, Y^2, Y^3, X^1, Z^1, R, R^1 and R^2 are as defined in formula (I), with a compound of formula (III), wherein R^5 is as defined in formula (I), using an appropriate coupling reagent (for example, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU)), in the presence of a base such as diisopropyl ethylamine, triethylamine or pyridine in an organic

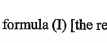
solvent (for example dimethylformamide, dichloromethane or acetonitrile) at a temperature in the range, for example, from 0 to 150°C [alternatively, the acid (III) may be activated by formation of an acid halide using a halogenating reagent such as oxalyl chloride or thionyl chloride; the acid chloride may then be reacted with a compound of formula (II) in the presense of a base such as diisopropyl ethylamine, triethylamine or pyridine in an organic solvent (for example dimethylformamide, dichloromethane or acetonitrile) at a temperature in the range, for example, from 0 to 150°C.];

(b) when R^4 represents COR^5 and R^5 represents C_1-C_6 alkyl substituted by $NR^{13}R^{14}$, reacting a compound of formula (IV)



(IV)

wherein L^2 represents a leaving group such as a halogen, mesylate or triflate, t is an integer from 1 to 6, and n, A, Y^1, Y^2, Y^3, X^1, Z^1, R, R^1 and R^2 are as defined in formula (I), with a compound of formula



(V)

wherein R^{13} and R^{14} are as defined in formula (I) [the reaction may be carried out in the presense of a base (for example diisopropyl ethylamine, triethylamine or pyridine) in an organic solvent such as dimethylformamide, dimethylsulphoxide or acetonitrile at a temperature, for example, in the range from 0 to 150°C];

(c) when R^4 represents a group SO_2R^5, reacting a compound of formula (II) as defined in (a) above with a compound of formula (VI), L^3-$S(O)_2$-R^5, wherein L^3 represents a leaving group (e.g. halogen) and R^5 is as defined in formula (I), in the presence of a base;

(d) when R^4 represents a group CO_2R^5, reacting a compound of formula (II) as defined in (a) above with a compound of formula (VII), L^4-C(O)-OR^5, wherein L^4 represents a leaving group (e.g. halogen) and R^5 is as defined in formula (I), in the presence of a base;

(e) when R^4 represents a group $SO_2NR^6R^7$, reacting a compound of formula (II) as defined in (a) above with a compound of formula (VIII), L^5-$S(O)_2$-NR^6R^7, wherein L^5 represents a leaving group (e.g. halogen) and R^6 and R^7 are as defined in formula (I), in the presence of a base;

or

(f) when R^4 represents a group $CONR^6R^7$, reacting a compound of formula (II) as defined in (a) above with a compound of formula (IX), L^6-C(O)-NR^6R^7, wherein L^6 represents a leaving group (e.g. halogen) and R^6 and R^7 are as defined in formula (I), in the presence of a base;

and optionally thereafter carrying out one or more of the following procedures:

- converting a compound of formula (I) into another compound of formula (I),
- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

In each of processes (c), (d), (e) and (f) above, the reaction is conveniently carried out in an organic solvent such as dimethylformamide, dichloromethane or acetonitrile at a temperature

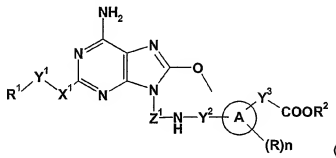
in the range from 0°C to 150°C. Suitable bases include diisopropyl ethylamine, triethylamine and pyridine.

A compound of formula (IV) may be prepared by reacting a compound of formula (II) with a compound of formula (X)

(X)

wherein L^2 and t are as defined in formula (IV). The reaction may be carried out using similar conditions to couple compounds of formulae (II) and (III).

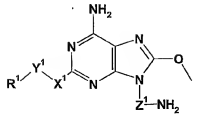
A compound of formula (II) may be obtained by the treatment of a compound of formula (XI)



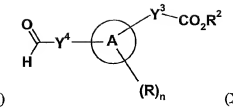
(XI)

wherein n, A, Y^1, Y^2, Y^3, X^1, Z^1, R, R^1 and R^2 are as defined in formula (I) with an acid. The reaction may be carried out in an organic solvent such as methanol, tetrahydrofuran or dioxane using either an inorganic acid such as hydrochloric acid, hydrobromic acid or sulfuric acid, or an organic acid such as trifluoroacetic acid.

A compound of formula (XI) may be obtained by the treatment of a compound of formula (XII)



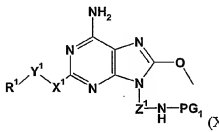
(XII)



(XIII)

wherein Z^1, X^1, Y^1 and R^1 are as defined in formula (I) with a compound of formula (XIII), wherein Y^4 represents a bond or a C_1-C_5 alkylene group and n, A, Y^3, R and R^2 are as defined in formula (I). The reaction may be carried out in the presense of a suitable reducing agent (for example sodium triacetoxyborohydride or sodium borohydride), in an organic solvent such as 1-methyl-2-pyrrolidinone, 1,2-dichloroethane, tetrahydrofuran or methanol at a temperature, for example, in the range from 0 to 150°C.

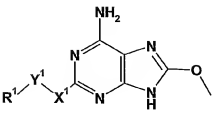
A compound of formula (XII) above may be obtained by treatment of a compound of formula



(XIV)

wherein Z^1 , X^1, Y^1 and R^1 are as defined in formula (I) and PG_1 represents a protecting group, e.g. phthalimide or Fmoc, which may be deprotected using hydrazine in ethanol or an organic base such as piperidine.

A compound of formula (XIV) may be prepared by reacting a compound of formula (XV)



(XV)

wherein X^1, Y^1 and R^1 are as defined in formula (I), with a compound of formula (XVI), L^7-Z^1-NH-PG_1, wherein L^7 represents a leaving group such as a halogen, mesylate or triflate, and Z^1 is as defined in formula (I) and PG_1 is as defined above. The reaction may conveniently be carried out in an organic solvent such as dimethylformamide, dimethylsulphoxide or acetonitrile in the presense of a base such as an alkali metal carbonate (for example sodium carbonate or potassium carbonate) or an alkaline earth metal carbonate (for example calcium carbonate), a metal hydroxide (for example sodium hydroxide or potassium hydroxide) at a temperature, for example, in the range from 0 to 150°C, preferably at room temperature (20°C).

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

The compounds defined in the formula (XV) may be obtained following the procedure described in the patent WO2005/092893.

Compounds of formulae (III), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XIII) and (XVI) are either commercially available, are well known in the literature or may be prepared using known techniques.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, trifluoroacetate, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Compounds of formula (I) is capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

The compounds of formula (I) and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as modulators of toll-like receptor (especially TLR7) activity, and thus may be used in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

2. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis;cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative or inflammatory

disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral , fungal, and bacterial;

4. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

5. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;

7. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

8. infectious diseases: virus diseases such as genital warts, common warts, plantar warts, respiratory syncytial virus (RSV), hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, para-influenza; bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, candida, aspergillus, cryptococcal meningitis, pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis.

Thus, the present invention provides a compound of formula (I) or a pharmaceutically-acceptable salt thereof as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

In particular, the compounds of the invention may be used in the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, respiratory syncytial virus (RSV), bacterial infections and dermatosis.

The invention still further provides a method of treating, or reducing the risk of, an obstructive airways disease or condition (e.g. asthma or COPD) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, the daily dosage of the compound of the invention, if inhaled, may be in the range from 0.05 micrograms per kilogram body weight (μg/kg) to 100 micrograms per kilogram body weight (μg/kg). Alternatively, if the compound is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight (μg/kg) to 100 milligrams per kilogram body weight (mg/kg).

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention (including pharmaceutically acceptable salts) may be administered by oral or nasal inhalation.

For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 micrometres (μm), and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C_8-C_{20} fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound of the invention with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and

titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of the above conditions.

The invention therefore further relates to combination therapies wherein a compound of the invention or a pharmaceutical composition or formulation comprising a compound of the invention is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases COPD, asthma and allergic rhinitis the compounds of the invention may be combined with agents such as tumour necrosis factor alpha (TNF-alpha) inhibitors such as anti-TNF monoclonal antibodies (for example Remicade, CDP-870 and adalimumab) and TNF receptor immunoglobulin molecules (such as Enbrel); non-selective cyclo-oxygenase COX-1/COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib,

parecoxib and etoricoxib); glucocorticosteroids (whether administered by topical,oral, intramuscular, intravenous, or intra-articular routes); methotrexate, lefunomide; hydroxychloroquine, d-penicillamine, auranofin or other parenteral or oral gold preparations.

The present invention still further relates to the combination of a compound of the invention and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention and a receptor antagonist for leukotrienes (LT B4, LTC4, LTD4, and LTE4) selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention and a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention and an anticholinergic agent including muscarinic receptor (M1, M2, and M3) antagonists such as atropine, hyoscine, glycopyrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention together with a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol.

The present invention further relates to the combination of a compound of the invention and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to the combination of a compound of the invention and a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12.

The present invention still further relates to the combination of a compound of the invention together with modulators of chemokine receptor function such as antagonists of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX3CR1 for the C-X3-C family.

The present invention still further relates to the combination of a compound of the invention together with a cytokine or modulator of cytokine function, including alpha-, beta-, and gamma-interferon; interleukins (IL) including IL1 to 15, and interleukin antagonists or inhibitors, including agents which act on cytokine signalling pathways.

The present invention still further relates to the combination of a compound of the invention together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (omalizumab).

The present invention further relates to the combination of a compound of the invention and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention further relates to the combination of a compound of the invention together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as

didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The anti-cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

(i) an antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii)antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The present invention will be further explained by reference to the following illustrative examples.

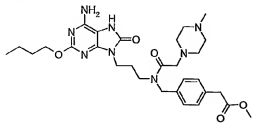
The following abbreviations are used;

EtOAc	ethyl acetate
DCM	dichloromethane
NMP	*N*-methylpyrrolidine
NBS	*N*-bromosuccinimide
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
THF	tetrahydrofuran
TFA	trifluoroacetic acid
K_2CO_3	potassium carbonate
$NaHCO_3$	sodium hydrogen carbonate
MeCN	acetonitrile
mCPBA	3-chloroperoxybenzoic acid (Aldrich 77% max)
rt	room temperature

h	hours
min	minutes
M	molar
N	normal
MS	mass spectrometry
APCI	atmospheric chemical ionisation method
ESI	electron spray ionisation method
NMR	nuclear magnetic resonance
HCl	hydrochloric acid
BOC	*tertiary*-butoxycarbonyl
HOBt	1-hydroxybenzotriazole
EDC	1-(3-dimethylamino propyl)-3-ethylcarbodiimide hydrochloride
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphonate

Unless otherwise stated organic solutions were dried over magnesium sulphate. RPHPLC denotes Reversed Phase Preparative High Performance Liquid Chromatography using Waters Symmetry C8, Xterra or Phenomenex Gemini columns using acetonitrile and either aqueous ammonium acetate, ammonia, formic acid or trifluoroacetic acid as buffer where appropriate. Column chromatography was carried out on silica gel. SCX denotes solid phase extraction with a sulfonic acid sorbent whereby a mixture was absorbed on a sulfonic acid sorbent and eluted with an appropriate solvent such as methanol or acetonitrile and then the free base product was eluted with aqueous ammonia/an appropriate solvent such as methanol or acetonitrile.

Example 1



Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(4-methylpiperazin-1-yl)acetyl]amino}methyl)phenyl]acetate

(i) 2-Chloro-9-(tetrahydro-2*H*-pyran-2-yl)- 9*H*-purin-6-amine

2,6-Dichloro-9-(tetrahydro-2*H*-pyran-2-yl)- 9*H*-purine (55g) was dissolved in 7N-aqueous ammonia in methanol (500ml) and heated at 100°C in a sealed flask for 6h. The reaction mixture was cooled to rt and left overnight. Filtration afforded the subtitle compound. Yield 40g.

^{1}H NMR δ ($CDCl_3$) 8.02 (1H, s), 5.94 (2H, brs), 5.71 (1H, dd), 4.15 - 4.22 (1H, m), 3.75 - 3.82 (1H, m), 1.27 - 2.12 (6H, m).

(ii) 2-Butoxy-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-amine

The product from step (i) (40g) was dissolved in 19%(w/w)-sodium butoxide in butanol (250ml). The reaction mixture was stirred under reflux for 6h. The resultant suspension was cooled to rt, diluted with water and extracted with diethyl ether. The combined organic phase was washed with water, dried and concentrated *in vacuo*. The subtitle compound was crystallized from diethyl ether/isohexane (1/1, 300ml) and obtained by filtration. Yield 19g.

^{1}H NMR δ ($CDCl_3$) 7.87 (1H, s), 5.56 - 5.68 (3H, m), 4.31 - 4.35 (2H, t), 4.14 - 4.17 (1H, m), 3.76 - 3.80 (1H, m), 1.49 - 2.08 (10H, m), 0.98 (3H, t).

(iii) 8-Bromo-2-butoxy-9-(tetrahydro-2*H*-pyran-2-yl) 9*H*-purin-6-amine

The product from step (ii) (30g) was dissolved in dry DCM (200ml). The solution was stirred at rt whilst *N*-bromosuccinimide (27g) was added portion wise. The mixture was stirred at rt overnight. 20%(w/v)-Sodium sulfate (200ml) was added and the separated aqueous phase extracted with DCM. The combined organic phase was washed with saturated $NaHCO_3$ solution and brine. After concentration *in vacuo*, the residue was dissolved in EtOAc, washed with water, brine and dried. The solution was filtered through silica gel. The filtrate was concentrated *in vacuo* and dissolved in a mixture of diethyl ether and isohexane (1/1, 200ml) to give the subtitle compound (26g). The solvent was removed to give a residue, which was purified by column chromatography (EtOAc/isohexane), which afforded 2.5g. The solids were combined to give the subtitle compound as a yellow solid. Yield 28.5g. mp 148-50°C

^{1}H NMR δ ($CDCl_3$) 5.59-5.64 (3H, m), 4.32 (2H, m), 4.17 (1H, m), 3.74 (1H, m), 3.08 (1H, m), 2.13 (1H, d), 1.48 - 1.83 (8H, m), 0.98 (3H, t).

(iv) 2-Butoxy-8-methoxy-9-(tetrahydro-2*H*-pyran-2-yl) 9*H*-purin-6-amine

Sodium (3.7g) was added to absolute methanol (400ml) under a nitrogen atmosphere. To this solution was added the product (28.5g) from step (iii) and the mixture was stirred at 65°C for 9h. The mixture was concentrated *in vacuo* and 500ml of water added. The aqueous phase was extracted with EtOAc and washed with brine and dried. The subtitle compound was obtained after crystallisation from diethyl ether. Yield 14.2g.

^{1}H NMR δ ($CDCl_3$) 5.51(1H, dd), 5.28 (2H, brs), 4.29 (2H, t), 4.11 - 4.14 (4H, m), 3.70 (1H, m), 2.76 - 2.80 (1H, m), 2.05 (1H, d), 1.47 - 1.81 (8H, m), 0.97 (3H, t).

(v) 2-Butoxy-8-methoxy-9*H*-purin-6-amine, TFA salt

The product from step (iv) (24g) was dissolved in absolute methanol (300ml) and 30ml of TFA was added. The reaction mixture was stirred at rt for 3 days and concentrated *in vacuo*. The subtitle compound was obtained as a white crystalline solid after trituration with methanol/EtOAc. Yield 21g.

^{1}H NMR δ (CD_3OD) 4.48 (2H, t), 4.15 (3H, s), 1.80 (2H, quintet), 1.50 (2H, sextet), 0.99 (3H, t).

(vi) 2-[3-(6-Amino-2-butoxy-8-methoxy-9*H*-purin-9-yl)propyl]-1*H*-isoindole-1,3(2*H*)-dione

The product from step (v) (15g) was dissolved in dry DMF (200ml) and 18g of K_2CO_3 added. After the suspension was stirred at rt for 15min, 2-(3-bromopropyl)-1*H*-isoindole-1,3(2*H*)-dione (14g) was added the the suspension vigorously stirred at rt for 10 h. The reaction mixture was extracted with EtOAc, washed with water and brine and dried. The subtitle compound was obtained after crystallisation from EtOAc/diethyl ether. Yield 16g.

^{1}H NMR δ (DMSO-d_6) 7.83 (4H, m), 6.73 (2H, brs), 4.06 (2H, t,), 4.01 (3H, s), 3.89 (2H, t), 3.58 (2H, t), 2.07-2.14 (2H, m), 1.55-1.62 (2H, m), 1.31-1.40 (2H, m), 0.90 (3H, t).

(vii) 9-(3-Aminopropyl)-2-butoxy-8-methoxy-9*H*-purin-6-amine

The product from step (vi) (1g) was dissolved in ethanol (10ml) and hydrazine monohydrate (1ml) was added and stirred at ambient temperature for 10h. The resultant was concentrated under reduced pressure and the residue suspended in DCM (10ml) and stirred for 1h. The suspension was filtered, washed with DCM. The solution was washed with water and dried. The solution was concentrated under reduced pressure to give the subtitled compound. Yield 700mg.

^{1}H NMR δ (DMSO-d_6) 6.77 (2H, brs), 4.16 (2H, t), 4.05 (3H, s), 3.89 (2H, t), 2.46-2.52 (2H, m), 1.61-1.76 (4H, m), 1.35-1.45 (2H, m), 0.92 (3H, t).

(viii) [4-({[3-(6-Amino-2-butoxy-8-methoxy-9*H*-purin-9-yl)propyl]amino}methyl)phenyl]acetic acid

The product from step (vii) (9.7g) and (4-formylphenyl)acetic acid (5.4g) were dissolved in THF (100ml) and stirred at rt for 4h. Sodium borohydride (1.9g) and 5 drops of methanol was added and stirred at a rt overnight. The mixture was quenched with water and concentrated under reduced pressure. Water was added and washed with diethyl ether. 0.1N-HCl was added to acidify the solution to pH 6. The suspension was filtered and the solid collected and dried under reduced pressure to give the subtitle compound. Yield 13g.

^{1}H NMR δ (DMSO-d_6) 7.14 – 7.22 (4H, m), 6.75 (2H, brs), 4.12 (2H, t), 4.03 (3H, s), 3.88 (2H, t), 3.62 (2H, s), 3.38 (2H, s), 1.34 - 2.47 (8H, m), 0.91 (3H, t).

(ix) Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]amino}methyl)phenyl]acetate

The product from step (viii) (13g) was dissolved in methanol (100ml) and 4N-HCl in dioxane (10ml) added. The reaction mixture was stirred at rt for 24h. The resultant was concentrated under reduced pressure and aqueous $NaHCO_3$ added to pH 8. The suspension was filtered and the solid collected and dried under reduced pressure to give the subtitle compound. Yield 11g.

^{1}H NMR δ (DMSO-d_6) 7.15 – 7.25 (4H, m), 6.35 (2H, brs6), 4.12 (2H, t), 3.71 (2H, t), 3.62 (3H, s), 3.62 (2H, s), 3.60 (2H, s), 2.47 (2H, m), 1.34 – 1.80 (6H, m), 0.90 (3H, t).

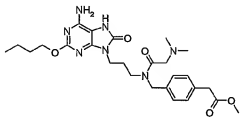
(x) Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(4-methylpiperazin-1-yl)acetyl]amino}methyl)phenyl]acetate

The product from step (ix) (200mg) was suspended in MeCN. Chloroacetyl chloride (0.02ml) added and the mixture stirred at rt for 4h. The mixture was concentrated under reduced pressure, piperazine (0.02 ml) in DMSO (1ml) was added and the mixture heated at 60 °C for 24h. The mixture was purified by RPHPLC. Yield 80mg.

^{1}H NMR δ (DMSO-d_6) 10.02 (1H, brs), 7.10 - 7.20 (4H, m), 6.30 (2H, brs), 4.52 (2H, m), 4.15 (3H, t), 3.60 - 3.66 (7H, m), 3.27 (4H, m), 2.98 (4H, m), 2.73 (4H, m), 2.61 (3H, s), 1.33 - 1.94 (6H, m), 0.92 (3H, t).

MS: APCI (+ve): 583 (M+H).

Example 2



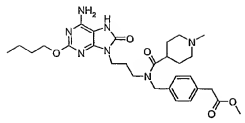
Methyl (4-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](*N*,*N*-dimethylglycyl)amino]methyl}phenyl)acetate

The product of example 1, step (ix) (200mg) was suspended in MeCN. *N*,*N*-dimethylglycyl chloride hydrochloride (110mg) and triethylamine (0.19ml) were added and the mixture stirred at rt for 10h. The mixture was purified by RPHPLC. Yield 100mg.

^{1}H NMR δ (DMSO-d_6) 7.07 - 7.22 (4H, m), 6.43 (2H, brs), 4.55 (2H, s), 4.13 (2H, t), 3.63 - 3.69 (4H, m), 3.60 (3H, s), 3.29 (2H, m), 3.01 (2H, s), 2.14 (2H, s), 1.31 - 1.97 (6H, m), 0.90 (3H, t).

MS: APCI (+ve): 528 (M+H).

Example 3



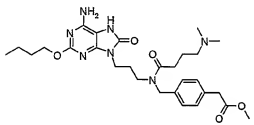
Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate

The title compound was prepared by the method of example 2 using 1-methylpiperidine-4-carbonyl chloride hydrochloride, yield 50mg.

^{1}H NMR δ (DMSO-d_6) 7.04 - 7.24 (4H, m), 6.45 (2H, brs), 4.51 (2H, s), 4.13 (2H, t), 3.60 - 3.65 (7H, m), 3.17 – 3.31 (4H, m), 2.66 (2H, s), 2.07 (3H, s), 1.35 – 2.02 (11H, m), 0.90 (3H, t).

MS: APCI (+ve): 568 (M+H).

Example 4



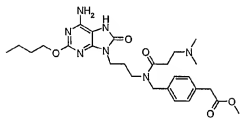
Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][4-(dimethylamino)butanoyl]amino}methyl)phenyl]acetate

The title compound was prepared by the method of example 2 using 4-(dimethylamino)butanoyl chloride hydrochloride, yield 30mg.

^{1}H NMR δ (DMSO-d_6) 7.05 - 7.24 (4H, m), 6.40 (2H, brs), 4.55 (2H, s), 4.12 (2H, t), 3.39 - 3.65 (7H, m), 3.23 (2H, m), 2.10 – 2.27 (4H, m), 2.04 (6H, s), 1.33 – 1.93 (8H, m), 0.91 (3H, t).

MS: APCI (+ve): 556 (M+H).

Example 5



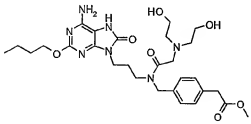
Methyl (4-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](*N*,*N*-dimethyl-β-alanyl)amino]methyl}phenyl)acetate

The title compound was prepared by the method of example 2 using *N*,*N*-dimethyl-β-alanyl chloride hydrochloride, yield 55mg.

^{1}H NMR δ (DMSO-d_6) 7.06 - 7.24 (4H, m), 6.40 (2H, brs), 4.51 (2H, s), 4.12 (2H, t), 3.62 - 3.69 (7H, m), 3.60 (3H, s), 3.23 (2H, m), 2.40 (4H, m), 2.05 (6H, s), 1.34 – 1.93 (6H, m), 0.90 (3H, t).

MS: APCI (+ve): 542 (M+H).

Example 6



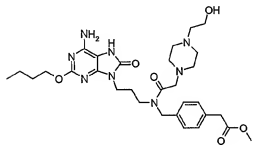
Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][*N*,*N*-bis(2-hydroxyethyl)glycyl]amino}methyl)phenyl]acetate

The title compound was prepared by the method of example 1 using 2,2'-iminodiethanol, yield 30mg.

^{1}H NMR δ (DMSO-d_6) 7.09 - 7.20 (4H, m), 4.59 (2H, brs), 4.22 (2H, m), 3.78 (2H, t), 3.64 (3H, s), 3.45 – 3.61 (10H, m), 2.71 (4H, m), 1.44 – 2.10 (6H, m), 0.95 (3H, t).

MS: APCI (+ve): 588 (M+H).

Example 7



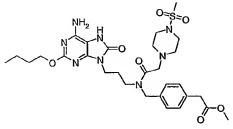
Methyl {4-[([3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]{[4-(2-hydroxyethyl)piperazin-1-yl]acetyl}amino)methyl]phenyl}acetate

The title compound was prepared by the method of example 1 using 2-piperazin-1-ylethanol, yield 52mg.

^{1}H NMR δ (DMSO-d_6) 9.87 (1H, brs), 7.06 - 7.21 (4H, m), 6.41 (2H, brs), 4.55 (2H, s), 4.22 (2H, m), 3.63 – 3.69 (4H, m), 3.60 (3H, s), 3.20 (2H, m), 3.04 (2H, s), 1.36 – 2.37 (18H, m), 0.90 (3H, t).

MS: APCI (+ve): 613 (M+H).

Example 8



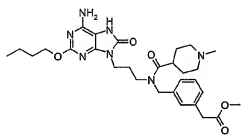
Methyl {4-[([3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]{[4-(methylsulfonyl)piperazin-1-yl]acetyl}amino)methyl]phenyl}acetate

The title compound was prepared by the method of example 1 using 1-(methylsulfonyl)piperazine, yield 25mg.

^{1}H NMR δ (DMSO-d_6) 7.07 - 7.24 (4H, m), 6.44 (2H, brs), 4.54 (2H, s), 4.12 (2H, m), 3.63 – 3.67 (4H, m), 3.60 (3H, s), 3.15 (2H, s), 3.03 (4H, m), 2.83 (2H, s), 2.40 (4H, m), 1.33 – 1.90 (6H, m), 0.90 (3H, t).

MS: APCI (+ve): 647 (M+H).

Example 9



Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate

(i) *tert*-Butyl [3-(6-amino-2-butoxy-8-methoxy-9*H*-purin-9-yl)propyl]carbamate

The product from example 1 step (v) (1.5g), 1.4g of K_2CO_3 and *tert*-butyl (3-bromopropyl)carbamate (1g) were heated at 50°C in DMF (10ml) for 3h. The reaction mixture was cooled to rt, extracted with EtOAc, washed with water and dried. The solvent

was removed to give a residue, which was purified by column chromatography (methanol/DCM), which afforded the subtitle compound. Yield 1.1g.

^{1}H NMR δ (DMSO-d_6) 6.82 (1H, t), 6.77 (2H, s), 4.17 (2H, t,), 4.04 (3H, s), 3.83 (2H, t), 2.90 (2H, m), 1.79 (2H, m), 1.65 (2H, m), 1.41 (2H, m), 1.37 (9H, s), 0.92 (3H, t).

(ii) 6-Amino-9-(3-aminopropyl)-2-butoxy-7,9-dihydro-8*H*-purin-8-one

The product from step (i) (1.1g) was dissolved in methanol/DCM (1/1, 40ml). 4N-HCl in dioxane (10ml) was added and the mixture stirred at rt for 20h. The resultant was concentrated under reduced pressure, which afforded the subtitle compound. Yield 0.9g.

^{1}H NMR δ (DMSO-d_6) 10.71 (1H, brs), 7.88 (2H, brs), 4.22 (2H, t,), 3.75 (2H, t), 2.77 (2H, m), 1.96 (2H, m), 1.36 – 1.70 (4H, m), 0.92 (3H, t).

(iii) Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]amino}methyl)phenyl]acetate

The product from step (ii) (3.1g) and methyl (3-formylphenyl)acetate (1.6g) were dissolved in NMP (30ml) and stirred for 15min. Sodium triacetoxyborohydride (3.7g) was added and the mixture stirred at rt for 20 h. After addition of methanol (1 ml), the mixture was purified by SCX, which afforded the subtitle compound. Yield 3.1g.

^{1}H NMR δ (DMSO-d_6) 7.27 – 7.21 (3H, m), 7.13 (1H, m), 6.46 (2H, brs), 4.12 (2H, t), 3.73 (2H, t), 3.70 (2H, s), 3.64 (2H, s), 3.61 (3H, s), 2.54 (2H, t), 1.82 (2H, m), 1.62 (2H, m), 1.37 (2H, m), 0.90 (3H, t).

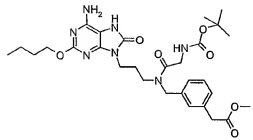
(iv) Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate

The product from step (iii) (0.1g), diisopropyl ethylamine (0.1ml) and 1-methylpiperidine-4-carboxylic acid hydrochloride (45mg) were dissolved in NMP (3ml) then HATU (130mg) added to the mixture. The mixture was stirred at rt for 5h then purified by SCX and RPHPLC, which afforded the title compound. Yield 70mg.

^{1}H NMR δ (DMSO- d_6) 7.23 (1H, t), 7.12 (1H, d), 7.03 (1H, s), 7.02 (1H, d), 6.15 (2H, brs), 4.50 (2H, s), 4.16 (2H, t), 3.65 (2H, t), 3.61 (2H, s), 3.60 (3H, s), 3.25 (2H, t), 2.68 (2H, m), 2.10 (3H, s), 1.86- 1.96 (2H, m), 1.63 (5H, m), 1.42 (4H, m), 0.91 (3H, t).

MS: APCI (+ve): 568 (M+1).

Example 10



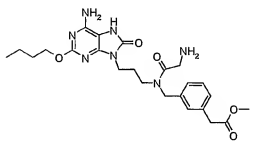
Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate

The title compound was prepared by the method of example 10 using *N*-(*tert*-butoxycarbonyl)glycine, yield 160mg.

^{1}H NMR δ (DMSO- d_6) 9.69 (1H, s), 7.27 (1H, m), 7.17 (1H, m), 7.09 (2H, m), 6.35 - 6.25 (1H, m), 6.14 (2H, brs), 4.54 (2H, s), 4.20 (2H, t), 3.83 (2H, d), 3.69 (2H, t), 3.65 (2H, s), 3.64 (3H, s), 3.31 (2H, t), 1.95 (2H, m), 1.68 (2H, m), 1.43 (2H, m), 1.40 (9H, s), 0.95 (3H, t).

MS: APCI (+ve): 600 (M+1).

Example 11



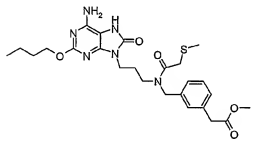
Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](glycyl)amino]methyl}phenyl)acetate

The product from example 10 (150mg) was dissolved in methanol (2ml) and 4N HCl in dioxane added. The mixture was stirred at rt for 3h and purified by RPHPLC, which afforded the title compound. Yield 20mg.

^{1}H NMR δ (DMSO- d_6) 7.24 (1H, m), 7.13 (1H, m), 7.05 (2H, m), 6.13 (2H, brs), 4.50 (2H, s), 4.17 (2H, s), 3.66 (2H, t), 3.62 (2H, s), 3.61 (3H, s), 3.33 (2H, s), 3.24 - 3.31 (2H, m), 1.92 (2H, m), 1.65 (2H, m), 1.40 (2H, m), 0.93 (3H, t).

MS: APCI (+ve): 500 (M+1).

Example 12



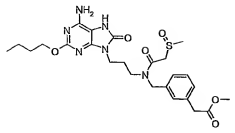
Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(methylthio)acetyl]amino}methyl)phenyl]acetate

The title compound was prepared by the method of example 10 using (methylthio)acetic acid, yield 170mg.

^{1}H NMR δ (DMSO- d_6) 7.24 (1H, m), 7.14 (1H, m), 7.07 (2H, m), 6.13 (2H, brs), 4.48 - 4.60 (2H, m), 4.17 (2H, t), 3.67 (2H, t), 3.62 (2H, s), 3.61 (3H, s), 3.33 (2H, s), 3.30 (2H, t), 2.09 (3H, s), 1.90 - 2.02 (2H, m), 1.65 (2H, m), 1.40 (2H, m), 0.92 (3H, t).

MS: APCI (+ve): 531 (M+1).

Example 13



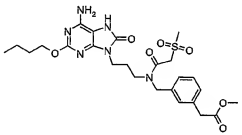
Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(methylsulfinyl)acetyl]amino}methyl)phenyl]acetate

The product from example 12 (150mg) was dissolved in DCM (10ml) and methanol (2ml) and mCPBA (0.1g) added. The mixture was stirred at rt for 3h then purified by RPHPLC, which afforded the title compound. Yield 50 mg.

^{1}H NMR δ (DMSO- d_6) 7.00 - 7.31 (4H, m), 6.14 (2H, brs), 4.46 - 4.70 (2H, m), 4.17 (2H, t), 3.92 (2H, s), 3.67 (2H, s), 3.61 (3H, s), 3.02 (4H, m), 2.62 (3H, s), 1.85 - 2.11 (2H, m), 1.65 (2H, m), 1.41 (2H, m), 0.93 (3H, t).

MS: APCI (+ve): 547 (M+1).

Example 14

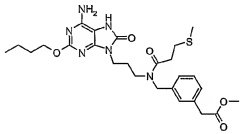


Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(methylsulfonyl)acetyl]amino}methyl)phenyl]acetate

The product from example 12 (150mg) was dissolved in DCM (10ml) and methanol (2ml) and mCPBA (0.1g) added. The mixture was stirred at rt for 3h then purified by RPHPLC, which afforded the title compound. Yield 40mg.

^{1}H NMR δ (DMSO- d_6) 7.05 - 7.39 (4H, m), 6.15 (2H, brs), 4.60 (2H, m), 4.35 (2H, m), 4.17 (2H, t), 3.68 (2H, s), 3.62 (3H, s), 3.11 (3H, s), 3.03 (4H, m), 1.84 - 2.05 (2H, m), 1.65 (2H, m), 1.41 (2H, m), 1.10 (3H, t).
MS: APCI (+ve): 563 (M+1).

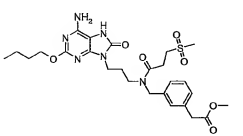
Example 15



Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylthio)propanoyl]amino}methyl)phenyl]acetate

The title compound was prepared by the method of example 10 using 3-(methylthio)propanoic acid, yield 130mg.
^{1}H NMR δ (DMSO- d_6) 7.25 (1H, m), 7.14 (1H, m), 7.07 (2H, m), 6.13 (2H, brs), 4.53 (2H, s), 4.17 (2H, t), 3.67 (2H, t), 3.62 (2H, s), 3.61 (3H, s), 3.31 (2H, t), 2.68 (2H, m), 2.58 (2H, m), 2.01 (3H, s), 1.99 - 1.89 (2H, m), 1.65 (2H, m), 1.41 (2H, m), 0.93 (3H, t).
MS: APCI (+ve): 545 (M+1).

Example 16



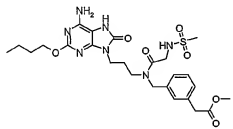
Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylsulfonyl)propanoyl]amino}methyl)phenyl]acetate

The title compound was prepared by the method of example 14 using the product from example 15, yield 60mg.

^{1}H NMR δ (DMSO- d_6) 7.24 (1H, m), 7.14 (1H, m), 7.06 (2H, m), 6.13 (2H, brs), 4.61 - 4.50 (2H, m), 4.16 (2H, t), 3.67 (2H, t), 3.62 (2H, s), 3.61 (3H, s), 3.34 (4H, m), 2.92 (3H, s), 2.80 (2H, t), 1.89 - 2.00 (2H, m), 1.65 (2H, m), 1.40 (2H, m), 0.92 (3H, t).

MS: APCI (+ve): 577 (M+1).

Example 17



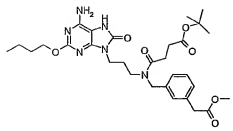
Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][*N*-(methylsulfonyl)glycyl]amino}methyl)phenyl]acetate

The product from example 11 (50mg) was dissolved in NMP (1ml), then pyridine (0.07ml) and methanesulfonic anhydride (29mg) added. The mixture was stirred at rt for 20h then purified by RPHPLC, which afforded the title compound. Yield 15mg

^{1}H NMR δ (DMSO- d_6) 7.25 (1H, m), 7.15 (1H, m), 7.07 (2H, m), 6.15 (2H, brs), 4.53 (2H, s), 4.17 (2H, t), 3.91 (2H, s), 3.67 (2H, t), 3.63 (2H, s), 3.62 (3H, s), 3.31 (2H, t), 2.92 (3H, s), 1.89 - 1.99 (2H, m), 1.65 (2H, m), 1.41 (2H, m), 0.93 (3H, t).

MS: APCI (+ve): 576 (M+1).

Example 18



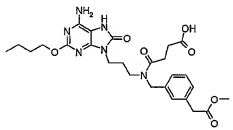
***tert*-Butyl 4-{[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-4-oxobutanoate**

The title compound was prepared by the method of example 10 using 4-*tert*-butoxy-4-oxobutanoic acid, yield 17mg.

^{1}H NMR δ (DMSO- d_6) 7.22 (1H, m), 7.12 (1H, m), 7.05 (2H, m), 6.11 (2H, brs), 4.51 (2H, s), 4.16 (2H, t), 3.65 (2H, t), 3.60 (2H, s), 3.60 (3H, s), 3.29 (2H, m), 2.50 (2H, m), 2.42 (2H, m), 1.85 - 1.98 (2H, m), 1.64 (2H, m), 1.39 (2H, m), 1.36 (9H, s), 0.91 (3H, t).

MS: APCI (+ve): 599 (M+1).

Example 19

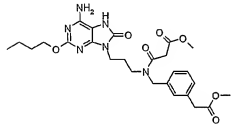


4-{[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-4-oxobutanoic acid

The product from example 18 (140mg) was dissolved in DCM (1ml) and TFA (0.2ml) added. The mixture was stirred at rt for 2h. The solution was washed with saturated aqueous $NaHCO_3$ solution and dried. The mixture was purified by RPHPLC, which afforded the title compound. Yield 80mg.

^{1}H NMR δ (DMSO- d_6) 9.66 (1H, s), 7.22 (1H, m), 7.12 (1H, m), 7.05 (2H, m), 4.52 (2H, brs), 4.16 (2H, t), 3.65 (2H, t), 3.61 (2H, s), 3.60 (3H, s), 3.29 (2H, m), 2.54 (2H, m), 2.46 (2H, m), 1.85 - 1.98 (2H, m), 1.64 (2H, m), 1.39 (2H, m), 0.91 (3H, t).
MS: APCI (+ve): 543 (M+1).

Example 20



Methyl 3-{[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-3-oxopropanoate

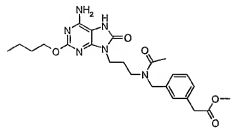
(i) *tert*-Butyl 3-{[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-3-oxopropanoate

The subtitle compound was prepared by the method of example 10 using 3-*tert*-butoxy-3-oxopropanoic acid. Yield 100mg.
MS: APCI (+ve): 585 (M+1).

(ii) Methyl 3-{[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-3-oxopropanoate

The product from step (i) (100mg) was dissolved in methanol (3ml) and 4N-HCl in dioxane added. The mixture was stirred at rt for 5h and purified by RPHPLC, which afforded the title compound. Yield 80mg
^{1}H NMR δ (DMSO- d_6) 9.68 (1H, s), 7.23 (1H, m), 7.13 (1H, m), 7.06 (2H, m), 6.11 (2H, brs), 4.51 (2H, s), 4.16 (2H, t), 3.65 (2H, t), 3.60 (6H, s), 3.27 (2H, t), 3.00 (2H, s), 2.99 (2H, m), 1.85 - 1.98 (2H, m), 1.64 (2H, m), 1.39 (2H, m), 0.91 (3H, t).
MS: APCI (+ve): 543 (M+1).

Example 21



Methyl [3-({acetyl[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]amino}methyl)phenyl]acetate

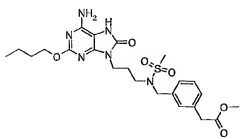
The product from example 20 step (i) (100mg) was dissolved in DCM (1ml) and TFA (0.2ml) added. The mixture was stirred at rt for 2h. The solution was washed with saturated aqueous $NaHCO_3$ and dried. The mixture was purified by RPHPLC, which afforded the title compound.

Yield 30mg

^{1}H NMR δ (DMSO- d_6) 7.01 - 7.29 (4H, m), 6.12 (2H, brs), 4.50 (2H, s), 4.15 (2H, t), 3.65 (2H, t), 3.61 (2H, s), 3.60 (3H, s), 3.26 (2H, t), 2.00 (3H, s), 1.83 - 1.99 (2H, m), 1.64 (2H, m), 1.39 (2H, m), 0.91 (3H, t).

MS: APCI (+ve): 485 (M+1).

Example 22



Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](methylsulfonyl)amino]methyl}phenyl)acetate

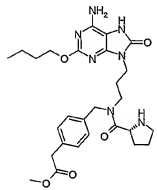
The title compound was prepared by the method of example 17 using product example 9 step (iii) (100mg) and methanesulfonic anhydride (76mg).

yield 60mg.

^{1}H NMR δ (DMSO- d_6) 7.33 - 7.49 (4H, m), 6.33 (2H, brs), 4.53 (2H, s), 4.38 (2H, t), 3.84 (2H, s), 3.82 (2H, m), 3.82 (3H, s), 3.37 (2H, t), 3.12 (3H, s), 2.10 (2H, m), 1.86 (2H m), 1.62 (2H, m), 1.14 (3H, t).

MS: APCI (+ve): 521 (M+1).

Example 23



(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)[2R]-propyl]-(pyrrolidine-2-carbonyl)-amino]-methyl}-phenyl)-acetic acid methyl ester

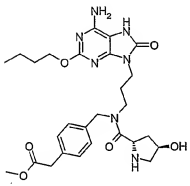
The product of example 1, step (ix) (300mg) and pyrrolidine-1,2-dicarboxylic acid 1-*(R)*-tert-butyl ester (146mg) were dissolved in DCM (10ml) and HATU (258mg) added. After 1h, more HATU (258mg) and *(R)*-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (146mg) were added to the miture. The mixture was stirred at rt for 16h and TFA (5ml) added and stirred for 4h. The reaction mixture was concentrated *in vacuo* to dryness then redissolved in methanol before being purified by RPHPLC, to give the title compound. Yield 19mg.

^{1}H NMR δ (DMSO- d_6) 8.19 (1H, s), 7.27 - 7.03 (5H, m), 6.46 (2H, d, J = 14.9 Hz), 4.71 - 4.49 (2H, m), 4.41 (1H, d), 4.20 - 4.04 (4H, m), 3.71 - 3.60 (4H, m), 3.47 - 3.33 (2H, m), 3.34 - 3.26 (2H, m), 3.26 - 3.18 (2H, m), 3.17 - 3.07 (2H, m), 2.92 - 2.81 (1H, m), 2.19 - 2.02 (2H,

m), 2.02 - 1.86 (2H, m), 1.82 - 1.69 (2H, m), 1.69 - 1.56 (2H, m), 1.45 - 1.32 (2H, m), 0.94 - 0.88 (3H, m).

MS: APCI (+ve): 540 (M+1).

Example 24



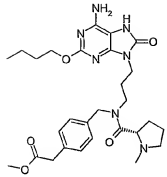
(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)-propyl][2S,4R](4-hydroxy-pyrrolidine-2-carbonyl)-amino]-methyl}-phenyl)-acetic acid methyl ester

The product of example 1, step (ix) (0.27 g) was dissolved in DCM (10ml) and treated with *(R)*-4-triethylsilanyloxy-pyrrolidine-1,2-dicarboxylic acid 1-*(S)*-tert-butyl ester (211mg) and HATU (232mg).The reaction was stirred at rt for 16h and TFA (2ml) added and stirred for 4h. The reaction mixture was concentrated to dryness *in vacuo* purifed by RPHPLC to give the title compound. Yield 114mg.

^{1}H NMR δ (DMSO- d_6) 8.22 (1H, s), 7.28 - 7.02 (4H, m), 6.46 (2H, d), 4.61 (1H, s), 4.60 - 4.36 (1H, m), 4.27 - 4.19 (2H, m), 4.17 - 4.06 (3H, m), 3.70 - 3.61 (4H, m), 3.34 - 3.23 (2H, m), 3.19 - 3.06 (2H, m), 2.00 - 1.86 (2H, m), 1.87 - 1.73 (2H, m), 1.70 - 1.56 (2H, m), 1.44 - 1.31 (2H, m), 0.96 - 0.84 (3H, m).

MS: APCI (+ve): 556 (M+1).

Example 25



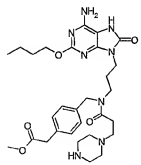
(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)-propyl][2S]-(1-methyl-pyrrolidine-2-carbonyl)-amino]-methyl}-phenyl)-acetic acid methyl ester

The product of example 1, step (ix) (0.43g), 1-methyl-pyrrolidine-2-carboxylic acid (0.13g) and HATU (0.37g) were stirred in DCM (5ml) at rt for 7 days. The reaction mixture was purified by SCX and RPHPLC, to give the title compound. Yield 24mg.

^{1}H NMR δ (DMSO- d_6) 9.92 (1H, d), 9.61 (1H, s), 7.30 - 7.03 (5H, m), 6.44 (2H, s), 4.67 - 4.56 (2H, m), 4.54 - 4.42 (2H, m), 4.15 - 4.05 (4H, m), 3.69 - 3.58 (4H, m), 2.84 - 2.73 (4H, m), 2.05 (3H, s), 2.10 - 1.97 (2H, m), 1.97 - 1.84 (2H, m), 1.86 - 1.73 (2H, m), 1.66 - 1.53 (2H, m), 1.37 - 1.24 (2H, m), 0.96 - 0.83 (3H, m).

MS: APCI (+ve): 554 (M+1).

Example 26



(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)-propyl]-(3-piperazin-1-yl-propionyl)-amino]-methyl}-phenyl)-acetic acid methyl ester

The product of example 1, step (ix) (0.27 g) was dissolved in DCM (10ml) and treated with 4-(2-carboxy-ethyl)-piperazine-1-carboxylic acid tert-butyl ester (0.16 g) and HATU (0.23g). The reaction was stirred at rt for 16h, before 2mls of TFA added. The mixture was purifed by RPHPLC, to give the title compound. Yield 3mg.

^{1}H NMR δ (DMSO- d_6) 9.93 (1H, d), 7.27 - 7.06 (4H, m), 6.52 - 6.41 (2H, m), 4.60 (1H, s), 4.48 (1H, s), 4.13 (2H, s), 3.71 - 3.59 (4H, m), 3.61 (3H, s), 3.43 - 3.16 (10H, m), 2.87 - 2.75 (2H, m), 2.02 - 1.91 (2H, m), 1.91 - 1.80 (2H, m), 1.68 - 1.58 (2H, m), 1.42 - 1.31 (2H, m), 0.91 (3H, t).

MS: APCI (+ve): 583 (M+1).

The compounds of Examples 27 to 103 were prepared by processes analogous to Example 1, step (x) using commercially available amines.

Example Number	Molecule IUPAC Name	M+1
27	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-[3-(1-piperidyl)propyl]piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	694
28	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[3-(diethylcarbamoyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate	667
29	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-phenyl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate	644
30	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	680
31	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(1-piperidyl)acetyl]amino]methyl]phenyl]acetate	568
32	ethyl 4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]piperazine-1-carboxylate	641

Example Number	Molecule IUPAC Name	M+1
33	2-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-(2-cyanoethyl)amino]acetic acid	611
34	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(benzyl-(2-dimethylaminoethyl)amino)acetyl]amino]methyl]phenyl]acetate	661
35	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-carbamoyl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate	611
36	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(3R)-3-hydroxypyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate	570
37	tert-butyl (2S)-1-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]pyrrolidine-2-carboxylate	654
38	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(2-cyanoethyl-(oxolan-2-ylmethyl)amino)acetyl]amino]methyl]phenyl]acetate	637
39	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(pyridin-4-ylmethyl)amino)acetyl]amino]methyl]phenyl]acetate	619
40	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-ethylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate	597
41	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(methyl-(2-pyridin-4-ylethyl)amino)acetyl]amino]methyl]phenyl]acetate	619
42	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyrrolidin-1-yl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate	637
43	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-carbamoylpyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate	597
44	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(3,6-dihydro-2H-pyridin-1-yl)acetyl]amino]methyl]phenyl]acetate	566

Example Number	Molecule IUPAC Name	M+1
45	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(2-hydroxyethyl)amino)acetyl]amino]methyl]phenyl]acetate	572
46	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(cyclohexyl-(2-hydroxyethyl)amino)acetyl]amino]methyl]phenyl]acetate	626
47	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(hydroxymethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate	598
48	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-aminoethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	612
49	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-hydroxyethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate	612
50	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[methyl-(1-methyl-4-piperidyl)amino]acetyl]amino]methyl]phenyl]acetate	611
51	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-benzyl-4-hydroxy-1-piperidyl)acetyl]amino]methyl]phenyl]acetate	674
52	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-cinnamylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate	685
53	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	657
54	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(3-dimethylaminopropyl-methyl-amino)acetyl]amino]methyl]phenyl]acetate	599
55	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(dimethylcarbamoylmethyl-methyl-amino)acetyl]amino]methyl]phenyl]acetate	599
56	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2R)-2-carbamoylpyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate	597

Example Number	Molecule IUPAC Name	M+1
57	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]acetyl]amino]methyl]phenyl]acetate	598
58	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-methyl-1,4-diazepan-1-yl)acetyl]amino]methyl]phenyl]acetate	597
59	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-morpholin-4-ylacetyl)amino]methyl]phenyl]acetate	570
60	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(3-hydroxyphenyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	661
61	methyl 2-[4-[[[2-[3-(acetyl-methyl-amino)pyrrolidin-1-yl]acetyl]-[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl]amino]methyl]phenyl]acetate	625
62	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(3S)-3-dimethylaminopyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate	597
63	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyridin-4-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate	646
64	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(3-dimethylaminopropyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	654
65	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-propan-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate	611
66	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(dimethylcarbamoylmethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	654
67	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2-hydroxy-2-phenyl-ethyl)-methyl-amino]acetyl]amino]methyl]phenyl]acetate	634
68	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(aminomethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate	597

Example Number	Molecule IUPAC Name	M+1
69	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(methyl-(2-methylaminoethyl)amino)acetyl]amino]methyl]phenyl]acetate	571
70	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-thiomorpholin-4-ylacetyl)amino]methyl]phenyl]acetate	586
71	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-phenylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate	645
72	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(1,3-dihydroisoindol-2-yl)acetyl]amino]methyl]phenyl]acetate	602
73	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-piperazin-1-ylacetyl)amino]methyl]phenyl]acetate	569
74	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(1-piperidyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate	651
75	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyridin-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate	646
76	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-hydroxy-1-piperidyl)acetyl]amino]methyl]phenyl]acetate	584
77	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(4-fluorophenyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	663
78	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-methyl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate	582
79	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(2,5-dihydropyrrol-1-yl)acetyl]amino]methyl]phenyl]acetate	552
80	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-benzothiazol-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate	702
81	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(ethoxycarbonylmethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate	654

Example Number	Molecule IUPAC Name	M+1
82	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-dimethylaminoethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	640
83	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-methylphenyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	659
84	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-ethylsulfonylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate	661
85	(2S,4R)-1-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]-4-hydroxy-pyrrolidine-2-carboxylic acid	614
86	(2S)-2-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-methyl-amino]-3-phenyl-propanoic acid	662
87	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate	584
88	3-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-(1,1-dioxothiolan-3-yl)amino]propanoic acid	690
89	3-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-cyclohexyl-amino]propanoic acid	654
90	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(2-ethylaminoethyl)amino)acetyl]amino]methyl]phenyl]acetate	599
91	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(3-ethylaminopropyl)amino)acetyl]amino]methyl]phenyl]acetate	613
92	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(3,4-dihydro-1H-isoquinolin-2-yl)acetyl]amino]methyl]phenyl]acetate	616

Example Number	Molecule IUPAC Name	M+1
93	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate	637
94	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-[(1-methyl-4-piperidyl)methyl]piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	680
95	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(methyl-prop-2-ynyl-amino)acetyl]amino]methyl]phenyl]acetate	552
96	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(1-methyl-4-piperidyl)-phenethyl-amino]acetyl]amino]methyl]phenyl]acetate	701
97	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(oxolan-2-ylmethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate	653
98	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(3R)-3-aminopyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate	569
99	tert-butyl (2R)-1-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]pyrrolidine-2-carboxylate	654
100	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyrimidin-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate	647
101	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-pyrrolidin-1-ylacetyl)amino]methyl]phenyl]acetate	554
102	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate	598
103	methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate	598

Biological Assay

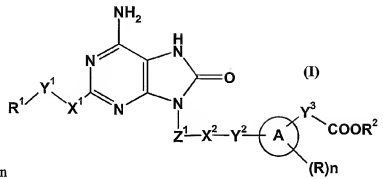
Human TLR7 assay

Recombinant human TLR7 was stably expressed in a HEK293 cell line already stably expressing the pNiFty2-SEAP reporter plasmid; integration of the reporter gene was maintained by selection with the antibiotic zeocin. The most common variant sequence of human TLR7 (represented by the EMBL sequence AF240467) was cloned into the mammalian cell expression vector pUNO and transfected into this reporter cell-line. Transfectants with stable expression were selected using the antibiotic blasticidin. In this reporter cell-line, expression of secreted alkaline phosphatase (SEAP) is controlled by an NFkB/ELAM-1 composite promoter comprising five NFkB sites combined with the proximal ELAM-1 promoter. TLR signaling leads to the translocation of NFkB and activation of the promoter results in expression of the SEAP gene. TLR7-specific activation was assessed by determining the level of SEAP produced following overnight incubation of the cells at 37°C with the standard compound in the presence of 0.1% (v/v) dimethylsulfoxide (DMSO). Concentration dependent induction of SEAP production by compounds was expressed as the log of the minimal effective concentration of compound to induce SEAP release (pMEC). For example

Compounds of Examples : 1, 4, 7 and 18 have pMEC >7.7

CLAIMS

1. A compound of formula (I)



wherein

R^1 represents hydrogen, hydroxyl, or a C_1-C_6 alkoxy, C_2-C_5 alkoxycarbonyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_6-C_{10} aryl, C_5-C_{10} heteroaryl or C_3-C_8 cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, a C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_2-C_5 alkoxycarbonyl, amino (NH_2), (mono)- C_1-C_6 alkylamino and (di)-C_1-C_6 alkylamino group;

Y^1 represents a single bond or C_1-C_6 alkylene;

X^1 represents a single bond, an oxygen, sulphur atom, sulphonyl (SO_2) or NR^3;

Z^1 represents a C_2-C_6 alkylene or C_3-C_8 cycloalkylene group, each group being optionally substituted by at least one hydroxyl;

X^2 represents NR^4;

Y^2 represents a single bond or C_1-C_6 alkylene;

Y^3 represents a single bond or C_1-C_6 alkylene;

n is an integer 0, 1 or 2;

R represents halogen or a C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 haloalkoxy, amino (NH_2), (mono)-C_1-C_6 alkylamino, (di)-C_1-C_6 alkylamino group or a C_3-C_8 saturated heterocyclic ring comprising a ring nitrogen atom and optionally one or more further heteroatoms independently selected from nitrogen, oxygen and sulphur, the heterocyclic ring being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_5 alkylcarbonyl and C_2-C_5 alkoxycarbonyl;

R^2 represents hydrogen or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_8 cycloalkyl group, each group being optionally substituted by one or more substituents independently selected from halogen, hydroxyl or a C_1-C_6 alkoxy, C_2-C_{10} acyloxy, amino (NH_2), (mono)- C_1-C_6 alkylamino, (di)-C_1-C_6 alkylamino group and a C_3-C_8 saturated heterocyclic ring comprising a ring nitrogen atom and optionally one or more further heteroatoms independently selected from nitrogen, oxygen and sulphur, the heterocyclic ring in turn being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_5 alkylcarbonyl and C_2-C_5 alkoxycarbonyl group;

R^3 represents hydrogen or C_1-C_6 alkyl;

R^4 represents CO_2R^5, SO_2R^5, COR^5, $SO_2NR^6R^7$ and $CONR^6R^7$;

R^5 independently represents

(i) a 3- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms comprising ring group NR^8, $S(O)_m$ or oxygen, each ring may being optionally substituted by one or more substituents independently selected from halogen, hydroxyl or a C_1-C_6 alkyl and C_1-C_6 alkoxy group, or

(ii) a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, cyano, C_1-C_6 alkyl,

C_1-C_3 haloalkyl, carboxyl, $S(O)_mR^9$, OR^{10}, CO_2R^{10}, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}SO_2R^9$, $NR^{10}CO_2R^9$, $NR^{10}COR^9$, or

(iii) a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_8 cycloalkyl group, each of which may be optionally substituted by one or more substituents independently selected from halogen, CN, C_3-C_8 cycloalkyl, $S(O)_pR^{12}$, OR^{13}, COR^{13}, CO_2R^{13}, $SO_2NR^{13}R^{14}$, $CONR^{13}R^{14}$, $NR^{13}R^{14}$, $NR^{13}SO_2R^{12}$, $NR^{13}CO_2R^{12}$, $NR^{13}COR^{12}$, $NR^{13}SO_2R^{12}$ or a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group or a heterocyclic ring, the latter three groups may be optionally substituted by one or more substituents independently selected from C_1-C_6 alkyl (optionally substituted by hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxycarbonyl, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, amido, C_1-C_6 alkylamido, di-C_1-C_6 alkylamido, $-OCH_2CH_2OH$, pyrrolidinyl, pyrrolidinylcarbonyl, furanyl, piperidyl, methylpiperidyl or phenyl), C_1-C_6 alkenyl (optionally substituted by phenyl), halogen, hydroxy, cyano, carboxy, amino, C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, amido, C_1-C_6 alkylamido, di-C_1-C_6 alkylamido, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylsulphonyl, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylcarbonylmethylamino, phenyl (optionally substituted by hydroxy, fluoro or methyl), pyrrolidinyl, pyridyl, piperidinyl, benzothiazolyl or pyrimidinyl;

R^6 represents hydrogen or a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl group or heterocyclic ring, each of which may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, OR^{15}, $S(O)_qR^{15}$, CO_2R^{16}, COR^{16}, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}COR^{17}$, $NR^{16}CO_2R^{15}$, $SO_2NR^{16}R^{17}$, $NR^{16}SO_2R^{15}$, or a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group or heterocyclic ring, the latter three groups being optionally substituted by one or more substituents independently selected from, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, halogen, $S(O)_qR^{15}$, CO_2R^{16}, COR^{16}, hydroxy or cyano; and

R^7 represents hydrogen, a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_3-C_8 cycloalkyl group, each group may be optionally substituted by one or more substituents independently selected from halogen, C_3-C_8 cycloalkyl, a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group, carboxy, cyano, OR^{15}, hydroxy or $NR^{18}R^{19}$, or

R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated or partially saturated heterocyclic ring, optionally containing further heteroatoms or heterogroups selected from nitrogen, $S(O)_m$ or oxygen. The heterocyclic ring, may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, carboxyl, cyano, OR^{20}, $NR^{21}R^{22}$, $S(O)_qR^{23}$, COR^{24}, CO_2R^{24}, $NR^{24}R^{25}$, $CONR^{24}R^{25}$, $NR^{24}COR^{25}$, $NR^{24}CO_2R^{23}$, $SO_2NR^{24}R^{25}$, $NR^{24}SO_2R^{23}$, C_6-C_{10} aryl , C_5-C_{10} heteroaryl group, heterocyclic ring, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_8 cycloalkyl group, the latter seven groups being optionally substituted by one or more substituents independently selected from halogen, hydroxyl, oxo, cyano, OR^{20}, $S(O)_qR^{23}$, COR^{24}, CO_2R^{24}, $NR^{24}R^{25}$, $CONR^{24}R^{25}$, $NR^{24}CO_2R^{23}$, $NR^{24}COR^{25}$, $SO_2NR^{24}R^{25}$, $NR^{24}SO_2R^{23}$, a heterocyclic ring or a C_6-C_{10} aryl or C_5-C_{10} heteroaryl group, the latter three groups being optionally substituted by one or more substituents independently selected from C_1-C_6 alkyl, halogen, hydroxy or cyano;

R^8 represents hydrogen, CO_2R^{26}, COR^{26}, SO_2R^{26}, C_1-C_6 alkyl or C_3-C_6 cycloalkyl group, each group may be optionally substituted by one or more substituents independently selected from halogen, hydroxyl, and $NR^{27}R^{28}$;

R^{10}, R^{11}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{26}, R^{27}, R^{28}, R^{29} or R^{30} each independently represents hydrogen, and a C_1-C_6 alkyl or C_3-C_6 cycloalkyl group;

R^{24} and R^{25} each independently represents hydrogen, and a C_1-C_6 alkyl or C_3-C_6 cycloalkyl group; or

R^{24} and R^{25} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated or partially saturated heterocyclic ring, optionally containing further heteroatoms or heterogroups selected from nitrogen, $S(O)_m$ or oxygen;

R^9, R^{12}, R^{15} and R^{23} represent C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R^{13} and R^{14} are defined as for R^6 and R^7 respectively;

R^{20} represents a C_1-C_6 alkyl optionally substituted by one or more substituents independently selected from halogen, hydroxyl or OR^{23};

m, p, q and r each independently represent an integer 0, 1 or 2; and

A represents a C_6-C_{10} aryl or C_5-C_{12} heteroaryl group;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein X^1 represents oxygen.

3. A compound according to claim 1 or claim 2, wherein Y^1 represents C_1-C_6 alkylene and R^1 represents hydrogen.

4. A compound according to any one of the preceding claims, wherein Z^1 represents C_2-C_6 alkylene

5. A compound according to any one of the preceding claims, wherein Y^2 represents C_1-C_6 alkylene.

6. A compound according to any one of the preceding claims wherein A represents C_6-C_{10} aryl.

7. A compound according to any one of the preceding claims wherein Y^3 represents C_1-C_6 alkylene.

8. A compound according to any one of the preceding claims wherein R^2 represents C_1-C_6 alkyl.

9. A compound according to any one of the preceding claims wherein R^4 represents SO_2R^5.

10. A compound according to any one of claims 1 to 8 wherein R^4 represents COR^5.

11. A compound of formula (I) according to claim 1 selected from:

Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(4-methylpiperazin-1-yl)acetyl]amino}methyl)phenyl]acetate,
Methyl (4-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](*N*,*N*-dimethylglycyl)amino]methyl}phenyl)acetate,
Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate,
Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][4-(dimethylamino)butanoyl]amino}methyl)phenyl]acetate,
Methyl (4-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](*N*,*N*-dimethyl-β-alanyl)amino]methyl}phenyl)acetate,
Methyl [4-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][*N*,*N*-bis(2-hydroxyethyl)glycyl]amino}methyl)phenyl]acetate,
Methyl {4-[([3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]{[4-(2-hydroxyethyl)piperazin-1-yl]acetyl}amino)methyl]phenyl}acetate,
Methyl {4-[([3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]{[4-(methylsulfonyl)piperazin-1-yl]acetyl}amino)methyl]phenyl}acetate,
Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate,
Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(1-methylpiperidin-4-yl)carbonyl]amino}methyl)phenyl]acetate,
Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](glycyl)amino]methyl}phenyl)acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(methylthio)acetyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(methylsulfinyl)acetyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][(methylsulfonyl)acetyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylthio)propanoyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(methylsulfonyl)propanoyl]amino}methyl)phenyl]acetate,

Methyl [3-({[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][*N*-(methylsulfonyl)glycyl]amino}methyl)phenyl]acetate,

tert-Butyl 4-{[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-4-oxobutanoate,

4-{[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-4-oxobutanoic acid,

Methyl 3-{[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl][3-(2-methoxy-2-oxoethyl)benzyl]amino}-3-oxopropanoate,

Methyl [3-({acetyl[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl]amino}methyl)phenyl]acetate,

Methyl (3-{[[3-(6-amino-2-butoxy-8-oxo-7,8-dihydro-9*H*-purin-9-yl)propyl](methylsulfonyl)amino]methyl}phenyl)acetate,

(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)[2R]-propyl]-(pyrrolidine-2-carbonyl)-amino]-methyl}-phenyl)-acetic acid methyl ester,

(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)-propyl][2S,4R](4-hydroxy-pyrrolidine-2-carbonyl)-amino]-methyl}-phenyl)-acetic acid methyl ester,

(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)-propyl][2S]-(1-methyl-pyrrolidine-2-carbonyl)-amino]-methyl}-phenyl)-acetic acid methyl ester,

(4-{[[3-(6-Amino-2-butoxy-8-oxo-7,8-dihydro-purin-9-yl)-propyl]-(3-piperazin-1-yl-propionyl)-amino]-methyl}-phenyl)-acetic acid methyl ester,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-[3-(1-piperidyl)propyl]piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[3-(diethylcarbamoyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-phenyl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Ethyl 4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]piperazine-1-carboxylate,

2-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-(2-cyanoethyl)amino]acetic acid,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(benzyl-(2-dimethylaminoethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-carbamoyl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(3R)-3-hydroxypyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

tert-Butyl (2S)-1-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]pyrrolidine-2-carboxylate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(2-cyanoethyl-(oxolan-2-ylmethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(pyridin-4-ylmethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-ethylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(methyl-(2-pyridin-4-ylethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyrrolidin-1-yl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-carbamoylpyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(3,6-dihydro-2H-pyridin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(2-hydroxyethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(cyclohexyl-(2-hydroxyethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(hydroxymethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-aminoethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-hydroxyethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[methyl-(1-methyl-4-piperidyl)amino]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-benzyl-4-hydroxy-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-cinnamylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(3-dimethylaminopropyl-methyl-amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(dimethylcarbamoylmethyl-methyl-amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2R)-2-carbamoylpyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-methyl-1,4-diazepan-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-morpholin-4-ylacetyl)amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(3-hydroxyphenyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[[2-[3-(acetyl-methyl-amino)pyrrolidin-1-yl]acetyl]-[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(3S)-3-dimethylaminopyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyridin-4-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(3-dimethylaminopropyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-propan-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(dimethylcarbamoylmethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2-hydroxy-2-phenyl-ethyl)-methyl-amino]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(aminomethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(methyl-(2-methylaminoethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-thiomorpholin-4-ylacetyl)amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-phenylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(1,3-dihydroisoindol-2-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-piperazin-1-ylacetyl)amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(1-piperidyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyridin-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-hydroxy-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(4-fluorophenyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-methyl-1-piperidyl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(2,5-dihydropyrrol-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-benzothiazol-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(ethoxycarbonylmethyl)-1-piperidyl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-dimethylaminoethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(2-methylphenyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-ethylsulfonylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

(2S,4R)-1-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]-4-hydroxy-pyrrolidine-2-carboxylic acid,

(2S)-2-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-methyl-amino]-3-phenyl-propanoic acid,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

3-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-(1,1-dioxothiolan-3-yl)amino]propanoic acid,

3-[[3-(6-Amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl-cyclohexyl-amino]propanoic acid,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(2-ethylaminoethyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(ethyl-(3-ethylaminopropyl)amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(3,4-dihydro-1H-isoquinolin-2-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-[(1-methyl-4-piperidyl)methyl]piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(methyl-prop-2-ynyl-amino)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(1-methyl-4-piperidyl)-phenethyl-amino]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[4-(oxolan-2-ylmethyl)piperazin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(3R)-3-aminopyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

tert-Butyl (2R)-1-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[[4-(methoxycarbonylmethyl)phenyl]methyl]carbamoyl]methyl]pyrrolidine-2-carboxylate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-(4-pyrimidin-2-ylpiperazin-1-yl)acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-(2-pyrrolidin-1-ylacetyl)amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

Methyl 2-[4-[[3-(6-amino-2-butoxy-8-oxo-7H-purin-9-yl)propyl-[2-[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]acetyl]amino]methyl]phenyl]acetate,

and pharmaceutically acceptable salts thereof.

12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 11 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A process for the preparation of a pharmaceutical composition as claimed in claim 12 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 11 with a pharmaceutically acceptable adjuvant, diluent or carrier.

14. A compound of formula (I) or a pharmaceutically-acceptable salt thereof as claimed in any one of claims 1 to 11 for use in therapy.

15. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 11 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of TLR7 activity is beneficial.

16. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 11 in the manufacture of a medicament for the treatment of allergic or viral diseases or cancers.

17. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 11 in the manufacture of a medicament for use in treating asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, cancer, hepatitis B, hepatitis C, HIV, HPV, respiratory syncytial virus (RSV), bacterial infections and dermatosis.

18. A method of treating, or reducing the risk of, a disease or condition in which modulation of TLR7 activity is beneficial which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 11.

19. A method of treating, or reducing the risk of, an allergic or viral disease or cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 11.

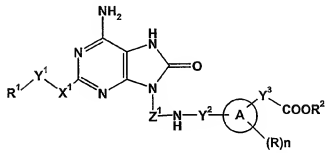
20. A method of treating, or reducing the risk of, an obstructive airways disease or condition which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 11.

21. A combination of a compound of formula (I) as claimed in any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, and one or more agents independently selected from:

- a non-steroidal glucocorticoid receptor agonist;
- a selective β_2 adrenoceptor agonist;
- a phosphodiesterase inhibitor;
- a protease inhibitor;
- a glucocorticoid;
- an anticholinergic agent;
- a modulator of chemokine receptor function; and
- an inhibitor of kinase function .

22. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 1 which comprises,

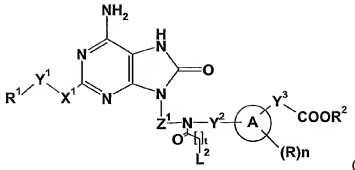
(a) when R^4 represents a group COR^5, reacting a compound of formula



(II)

wherein n, R, R^1, R^2, A, X^1, Z^1, Y^1, Y^2 and Y^3 are as defined in formula (I), with a compound of formula (III), R^5-C(O)-L^1, wherein L^1 represents halogen or hydroxy and R^5 is as defined in formula (I), in the presence of a base or a coupling reagent as required;

(b) when R^4 represents a group COR^5 and R^5 represents a group C_1-C_6 alkyl-$NR^{13}R^{14}$, reacting a compound of formula



(IV)

wherein L^2 represents a leaving group, t is an integer from 1 to 6, and n, A, Y^1, Y^2, Y^3, X^1, Z^1, R, R^1 and R^2 are as defined in formula (I), with a compound of formula (V), $NHR^{13}R^{14}$, wherein R^{13} and R^{14} are as defined in formula (I), in the presence of a base;

(c) when R^4 represents a group SO_2R^5, reacting a compound of formula (II) as defined in (a) above with a compound of formula (VI), L^3-$S(O)_2$-R^5, wherein L^3 represents a leaving group and R^5 is as defined in formula (I), in the presence of a base;

(d) when R^4 represents a group CO_2R^5, reacting a compound of formula (II) as defined in (a) above with a compound of formula (VII), L^4-C(O)-OR^5, wherein L^4 represents a leaving group and R^5 is as defined in formula (I), in the presence of a base;

(e) when R^4 represents a group $SO_2NR^6R^7$, reacting a compound of formula (II) as defined in (a) above with a compound of formula (VIII), L^5-$S(O)_2$-NR^6R^7, wherein L^5 represents a leaving group and R^6 and R^7 are as defined in formula (I), in the presence of a base;

or

(f) when R^4 represents a group $CONR^6R^7$, reacting a compound of formula (II) as defined in (a) above with a compound of formula (IX), L^6-C(O)-NR^6R^7, wherein L^6 represents a leaving group and R^6 and R^7 are as defined in formula (I), in the presence of a base;

and optionally thereafter carrying out one or more of the following procedures:

- converting a compound of formula (I) into another compound of formula (I),
- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000651

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-20
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 18-20 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

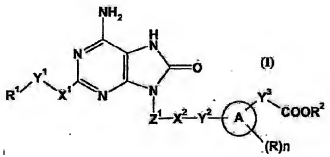
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention provides 8-oxoadenine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy. The 8-oxoadenine derivatives act as modulators of Toll-like Receptor (TLR) 7 and thus may be used in the treatment of asthma, hepatitis, allergic diseases, viral and bacterial infection as well as cancer.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000651

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1550662 A1 (SUMITOMO PHARMACEUTICALS COMPANY, LIMITED), 6 July 2005 (06.07.2005), page 86, Comp Ex 1,3; page 87, Comp Ex 5-6, page 97, Comp Ex 243, 247, claims 1,37,40-42	1-17,21-22
	--	
A	LEE, JONGDAE et al, "Activation of anti-hepatitis C virus responses via Toll-like receptor 7", PNAS, 7 February 2006, vol. 13, no. 6, page 1828 - page 1833; page 1828, column 2, line 13 - line 22, abstract	1-17,21-22
	--	
P,X	WO 2007031726 A1 (ASTRAZENECA AB), 22 March 2007 (22.03.2007), whole document	1-17,21-22
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2007	09-10-2007
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2007/000651

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007034173 A1 (ASTRAZENECA AB), 29 March 2007 (29.03.2007), the whole document	1-17,21-22
	--	
P,X	WO 2007034881 A1 (DAINIPPON SUMITOMO PHARMA CO., LTD.), 29 March 2007 (29.03.2007), whole document	1-17,21-22
	--	
P,X	WO 2007034882 A1 (DAINIPPON SUMITOMO PHARMA CO., LTD.), 29 March 2007 (29.03.2007), the whole document	1-17,21-22
	--	
P,X	WO 2007034917 A1 (DAINIPPON SUMITOMO PHARMA CO., LTD.), 29 March 2007 (29.03.2007), whole document	1-17,21-22
	--	
P,X	EP 1728793 A1 (DAINIPPON SUMITOMO PHARMA CO., LTD.), 6 December 2006 (06.12.2006), whole document	1-17,21-22
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International patent classification (IPC)

C07D 473/18 (2006.01)
A61K 31/522 (2006.01)
A61P 11/00 (2006.01)
A61P 11/06 (2006.01)
A61P 17/00 (2006.01)
A61P 27/14 (2006.01)
A61P 31/14 (2006.01)
A61P 31/18 (2006.01)
A61P 31/20 (2006.01)
A61P 35/00 (2006.01)
A61P 37/08 (2006.01)

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Use the application number as username.
The password is **TVRYWJLXEO**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

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				NO	20052038 A	24/05/2005
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				KR	20050062562 A	23/06/2005
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				ZA	200501920 A	07/09/2005
WO	2007031726	A1	22/03/2007	NONE		
WO	2007034173	A1	29/03/2007	NONE		
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